changes in the number of platelets play in this alteration remains to be settled.

SUMMARY

By means of a specific test whereby finer analysis of the velocity of coagulation is possible it is shown that an acceleration occurs during uncomplicated bed rest, in acute inflammatory conditions, following operation and in the presence of severe hæmorrhage.

Evidence is presented to support the view that the test gives an indirect means of measuring the thromboplastin factor of the process of coagulation and that it is upon an increase of this factor that acceleration depends.

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A SIMPLE OFFICE TEST FOR UTERINE CANCER DIAGNOSIS*

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AN office procedure to enable early diagnosis of uterine cancer is now available. Such a test has been made possible largely by the work of Papanicolaou and Traut,[1] in which the vaginal smear technique is employed. Their results would appear to indicate a fairly high degree of accuracy. This conclusion has recently been corroborated by the work of Meigs *et al.*[2] It has been found in our clinic, and the above-mentioned investigators have also stated, that in many cases intensive study of several slides is required to arrive at the correct diagnosis when the smears are taken directly from the vagina. A simple modification of this technique would appear to render the test more rapid and more efficient. This modification consists in taking the smear directly from the external os of the cervix. Here the concentration of cancer cells is greater. In our series of cases, smears from the vagina were compared with smears from the external os, and in both cervical and fundal carcinoma a much greater concentration of cancer cells was consistently present in the latter group.

The statement that uterine cancer may be accurately diagnosed by the vaginal or cervical os smear probably arouses an initial skepticism in the minds of many. The idea at first glance perhaps appears somewhat far-fetched. It may be the impression of some that the vaginal smears consist only of vaginal epithelial cells scraped off from the vaginal mucosa, and that the diagnosis of cancer is attempted from the morphological and staining characteristics of the vaginal cells themselves. It is difficult to conceive how any diagnosis of uterine cancer could be made from a study of these cells alone. When one considers, however, that the vaginal secretions contain not only vaginal cells but also cells thrown off from the cervix, the endometrium, and the tubal epithelium, the horizon of the diagnostic possibilities might appear to be broadened. Consider, further, that, while the epithelium of the genital tract is normally exfoliated at a certain rate, the cells from a

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malignant ulcer at any part of the genital tract will be desquamated at a greatly accelerated rate. There will be increased secretion, accompanied by increased sloughing of the superficial cells, and bleeding. Whenever such a lesion will produce "spotting", look for the cancer cells in the secretion! It is by the study of these cells, carried down by the blood and discharge to the vaginal receptacle, that more information as to their growth activities may be gleaned.

The vaginal smear test for cancer may be considered a surface biopsy of the cells and cell clumps being shed by the genital tract. The finding of cancer cells in these secretions would appear to be strong presumptive evidence of cancer. The mere finding of the cells does not always point to the origin of the growth. However, as malignant growths of the genital tract are chiefly cervical or fundal, these sites should be the first subjected to tissue biopsy. Cancer of the vagina, cervix, endometrium or tubes may cast off cells into the vagina and thus give evidence of its presence. It is felt, at the present time, that the diagnosis of cancer cells in the smears should be confirmed by biopsy before operation or radio-therapy.

Papanicolaou and Traut[1] first identified and described the cancer cells in the vaginal secretions. In their original series they found genital cancer in 179 cases, only 3% of which failed to show cancer in the smears. More recently, Meigs[2] reports studying 62 cases of cancer in which he was able to diagnose cancer by the smear in 60 of these. Of 153 negative cases, positive smears were reported in 4%, an error of 2.6%.

A significant factor favouring the smear technique is the relative speed with which a diagnostic report may be made. As compared with a biopsy report a smear diagnosis may be made in half an hour, while a biopsy may take one or two days. It may be that with further proof of the reliability of this technique, it may be preferred to the frozen section.

Uterine cancer annually takes a toll of 26,000 lives in the United States. There has been little improvement in these statistics during the last 20 years. According to the findings of Bigelow and Lombard,[3] the average time lost in uterine cancer cases from the first signs of bleeding to the time of operation is almost eight months. Therefore, delay in diagnosis is a major factor in maintaining the high mortality rate. So often when the patient in the menopausal age presents herself with irregular bleeding the physician finds it impossible to differentiate between the more frequent menopausal changes and a beginning malignant growth.

A simple office test which may be taken by any physician when the first signs of spotting are reported should be of great value in speeding up the diagnosis. It is relatively easy to diagnose cancer clinically, once the growth is advanced, but it is not so simple when there is nothing abnormal palpable or visible to be found. This is the stage when diagnosis would allow more certain cure.

While it may not be justified to say that every woman manifesting spotting of blood should be hospitalized and subjected to the expense of a biopsy or curettage, every such case should have the benefit of a vaginal smear examination, and any positive or doubtful case should have a biopsy without delay. Here the value of the smear diagnosis is greatest, as it enables the physician to sort the "wheat from the chaff" at the time of the initial examination, without necessitating recourse to the so frequent "wait and see" policy.

As an office test the smear may be compared to a Wassermann test, being taken in the office, the slide placed in solution to be forwarded to the laboratory or hospital for precise staining, then to the skilled microscopist for the all-important interpretation.

TECHNIQUE

The technique for taking smears is as follows:

A vaginal smear is first taken, following the technique described by Papanicolaou. A second smear is then taken from the external os of the cervix, using a bi-valve speculum. The pipette used is 6 inches long, slightly curved at the end and is attached to a two and a half-inch rubber suction bulb. It is important for the pipette to be clean and dry, and the patient should not have been examined vaginally or had a douche on the day the smears are taken.

When the first smear is taken, the bulb is compressed, the labia are separated with the fingers, and the pipette is introduced into the vagina as far as possible. The bulb is then released, and the pipette is withdrawn slowly along the floor of the vagina. The secretion is then forced out of the pipette on to a clean, dry slide, previously dated and identified. The slide

is then promptly immersed in a bottle containing fixative solution consisting of one-half ether and one-half alcohol (95%). Immediate fixation is most desirable, as drying of the smear causes a loss of cellular detail. Slides must be left in the fixative for at least 5 minutes, but they may be left in the solution for 1 to 2 weeks.

The smear from the external os is taken with the aid of a bi-valve speculum. The cervix is adequately exposed, and the mucus from the region of the external os is sucked into a second pipette. The secretion is again transferred to a slide and is immediately placed in the fixative solution. It is thought to be of advantage to take both smears, the vaginal and cervical, as the former gives a more accurate cornification count (œstrogen level estimation). After the slides have been put through the alcohols (70-50%), they are placed in distilled water. They are stained for 3 minutes in Harris' hæmatoxylin and dipped 4 times in 0.5% solution of hydrochloric acid. They are then washed in running tap water, and placed in a 0.5% solution of lithium carbonate for 1 minute. Again the slides are washed in running tap water, then rinsed in distilled water, and run up through the alcohols (50, 70, 80-95%). Then, after staining for 1 minute in a 0.5% solution of orange G in 95% alcohol, the smears are washed in two changes of 95% alcohol. They are stained in EA 36' for 2 minutes, washed in three changes of 95% alcohol, run through absolute alcohol to xylol, and mounted in Canada balsam.

Certain specific criteria of diagnosis may be mentioned. Just as different cancer growths manifest extreme variability in morphology and pattern, so the individual cells or cell clumps show all grades of atypicalness from the normal to the bizarre and even picturesque forms. In cancer of the cervix the cells vary in size and shape and form, and many atypical basal, squamous cells are seen. Various elongated or tadpole cells are found; multiple nuclei, and vacuolation occur. The nuclei show the most significant variations, in size, shape, and in the pattern of the chromatin granules. The staining is variable, some cells appearing acidophilic, others basophilic, while hyperchromatic staining is common too, as it must be remembered these cells are dead and degenerating desquamated cells. The staining may be affected, too, by the fluctuation of the vaginal acidity associated with infection or infestation. Trichomoniasis is not uncommon in the cancerous leucorrhœa. The acidophilic staining in cancer, representing cornification, is worthy of more study to determine its relation to the secretion of œstrogen in the post-menopausal women. In some cases hyperœstrinism is found in these women along with cancer (Case 2). Mitosis is sometimes, though rarely, found.

The presence of blood or blood-pigment crystals is always a prerequisite to a positive diagnosis. Either blood cells or fern-like orange or green deposits of pigment may be found in a positive case.

Leucocytes are usually quite numerous, either singly or in clumps. Eosinophils, rare in normal smears, are more numerous in cancer. Tissue phagocytic cells or histiocytes are usually to be found. While they may occur in benign conditions, they are frequently more numerous and more active in malignancy. Red blood cells, leucocytes and vacuoles are often found in their cytoplasm. It must be remembered that most of the cells found in smears are normal and the smaller the growth, and the earlier the test, the more assiduous must be the search for the cancer cell. This search will be facilitated by the modified technique described in this paper. In many lesions, however, the diagnosis may be made at a glance just as the pathologist may, on examining the biopsy. Aberrant cell types are numerous in advanced cases. In younger women the normal squamous, cornified and precornified cells predominate, while in older women basal cells are more numerous. The cancer cells are often found lurking in the shadows of these normal cells, as ghosts half-hidden in the background.

In fundal carcinoma the criteria are generally quite similar. The presence of blood, leucocytes and histiocytes is constant. Many cases will show specific cellular variations as compared with squamous growths. The atypical basal cells do not occur characteristically. There is less variation in the size of cells, but the nuclei vary greatly in size, nuclear gigantism being not uncommon. The abnormal cells are often found in clumps. In some cases (*e.g.* case 1) the cells resemble endometrial glandular epithelial cells sufficiently to render a presumptive diagnosis of adenocarcinoma possible in contrast to a squamous carcinoma of the cervix. In other cases the cellular morphology is so bizarre as

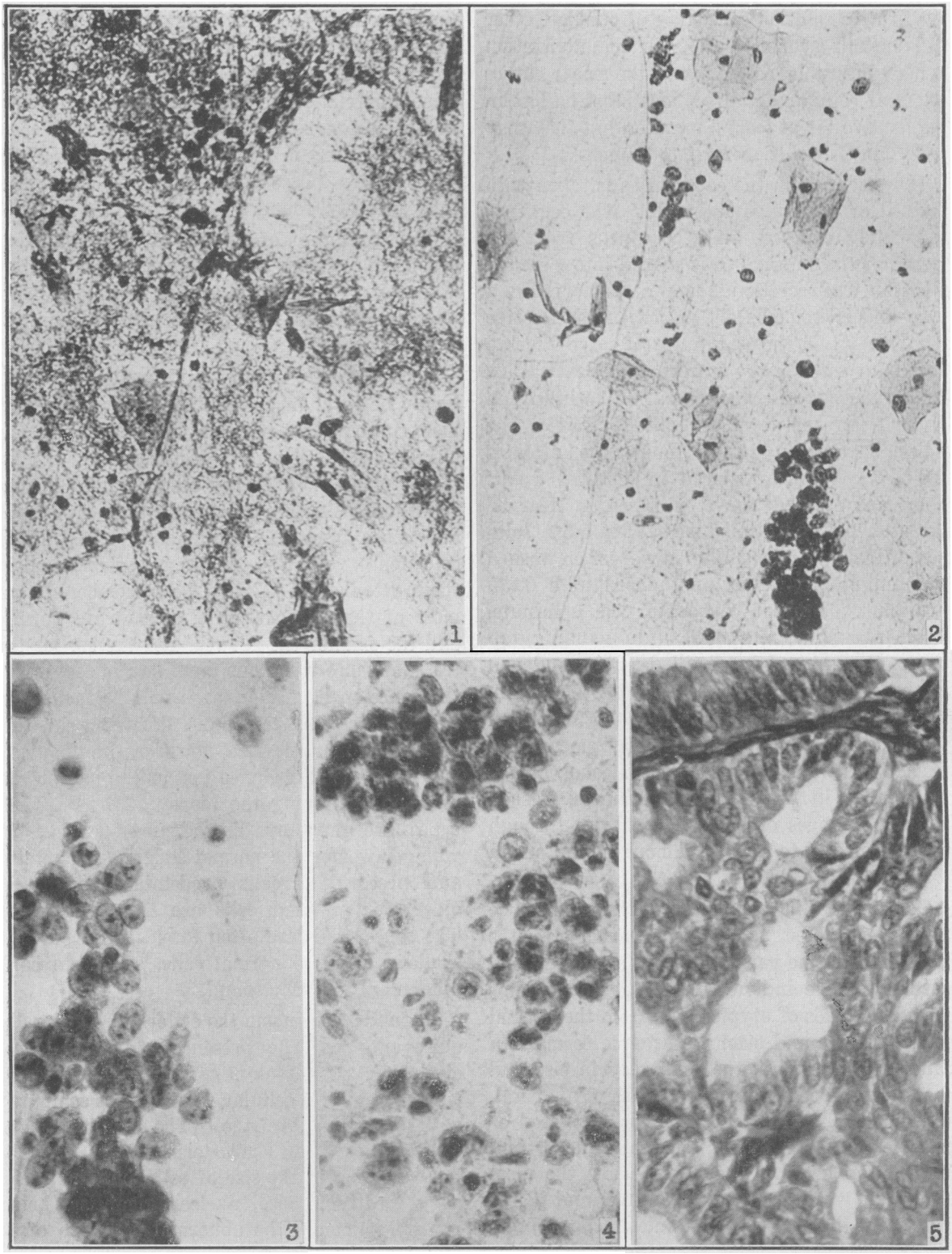

Fig. 1. (Case 1).—Vaginal smear showing scattered cancer cells, leucocytes, squamous epithelial cells and red blood cells. **Fig. 2.** (Case 1).—External os smear, showing greater concentration of cancer cells amongst scattered leucocytes, squamous cells and red blood cells. **Fig. 3.** (Case 1).—High power of (2) showing cancer cells with large nuclei containing numerous chromatin bundles. **Fig. 4.** (Case 1).—Smear taken directly from surface of growth at operation. The cells appear better preserved, but show the same morphology as the cells found in the preoperative smears. **Fig. 5.** (Case 1).—Biopsy of glandular area of growth. Other areas showed sheets of cells penetrating myometrium with metastases in ovaries.

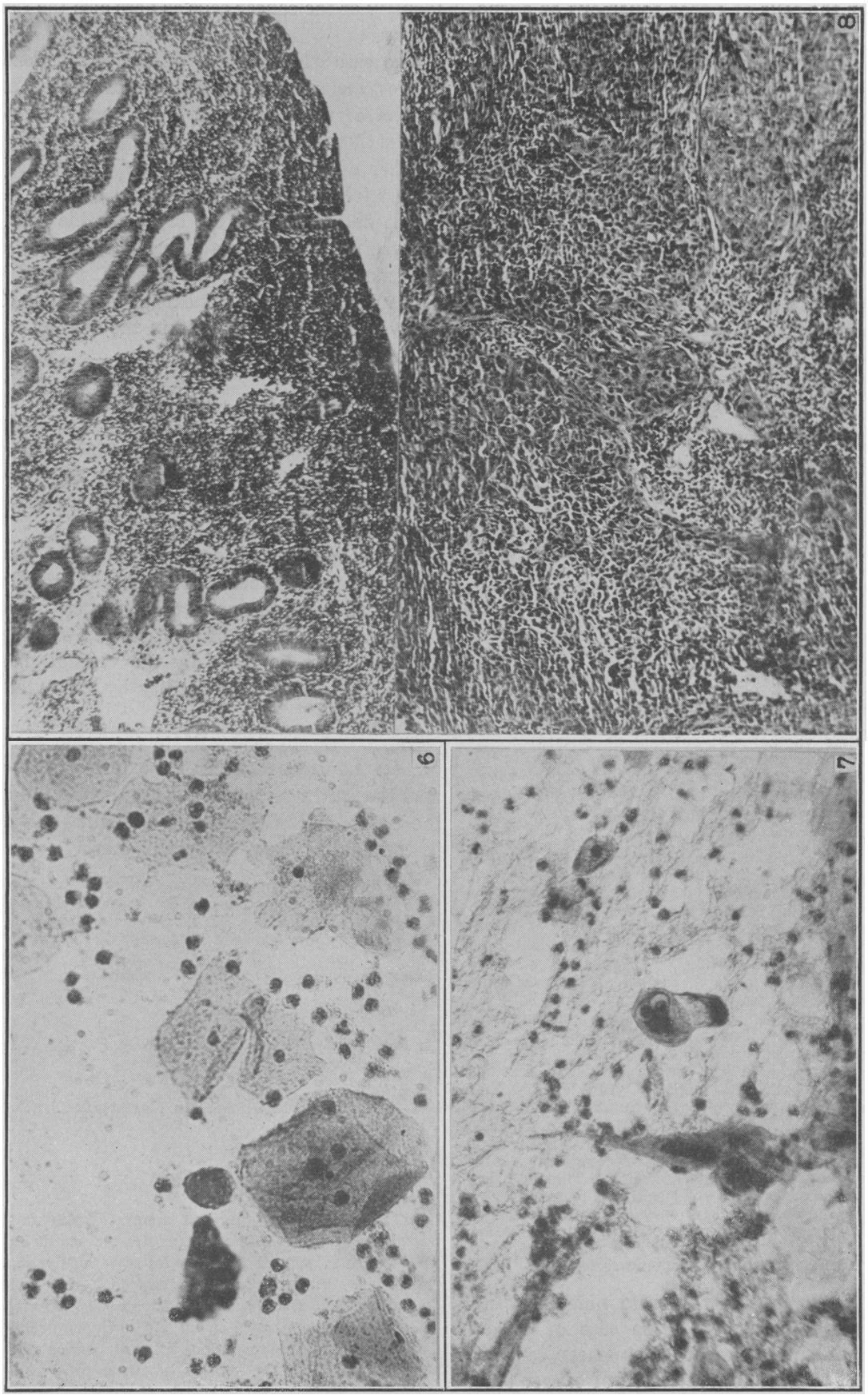

Fig. 6. (Case 2).—Vaginal smear showing rare cancer cells amongst leucocytes, red blood cells and squamous epithelial cells (cornified).
Fig. 7. (Case 2).—External os smears showing numerous atypical squamous cancer cells. Note elongated nuclei in spindle-shaped cells.

Fig. 8. (Case 2).—Biopsy of squamous growth. Note adjacent endometrial curetting showing actively regenerating glands in this patient of 68 years. These glands with the young cornified epithelial cells in (6) indicate some active œstrogenic secretion.

to render the cells of either squamous or adenocarcinoma indistinguishable. This runs parallel with the same finding in different growths when studied pathologically from the tissue biopsy.

The value of the smears would appear to lie first and foremost in the early diagnosis made possible. Secondly, they are important in following the progress of lesions following operation or radiotherapy. The presence of cancer cells persisting long after treatment is a bad sign, but their absence cannot but be interpreted as a ray of prognostic optimism.

In this clinic we have investigated 75 cases for cancer. Forty of these were proved to be cancer by biopsy and of these 38 showed cancer cells in the smear. Two representative cases have been chosen from this series for purposes of illustration, the first a case of fundal adenocarcinoma, and the second a case of squamous carcinoma of the cervix.

CASE REPORTS

CASE 1

The patient, a female of 57 years, complained of bleeding irregularly for 12 years, associated with severe dysmenorrhœa. Pelvic examination revealed the presence of a uterine myoma complicated by sepsis, with a recent exacerbation of vaginal bleeding. The severity of the infection contraindicated diagnostic curettage. At this time vaginal and external os smears showed clearly a positive diagnosis of cancer, suggesting a fundal origin. Since the myoma called for major surgical therapy, whether associated with cancer or not, a panhysterectomy was performed and the presence of the fundal adenocarcinoma was confirmed.

CASE 2

The patient, a female of 68 years, was admitted complaining of spotting for 2 months. She had had amenorrhœa since the age of 44 years, following the removal of an ovarian cyst. Vaginal smears showed occasional cancer cells, while the external os smear exhibited large numbers of atypical cells and many bizarre forms characteristic of malignancy. Cervical biopsy showed squamous carcinoma. No major operation was performed in this case, obesity indicating radio-therapy in preference to surgery.

This particular case has certain individual features of unusual interest. Although 68 years of age, her vaginal smear shows a cornification count of 30%. (The usual post-menopausal count would be near zero.) The cervical os smear gave a lower cornification count of 7%. The relatively high degree of cornification suggests some active œstrogenic secretion. This is borne out by the fact that the cells exhibit the morphology of youth. The endometrial biopsy confirms this, showing actively regenerating endometrium! Such a finding would appear to favour the theory of some etiological association of cancer and œstrogenic secretion.

The illustrations demonstrate numerous features of significance. In the case of fundal adenocarcinoma the external os smear contains a definitely higher concentration of cancer cells. The direct smear from the tumour confirms the identity of the cancer cells as does also the tissue biopsy.

The case of carcinoma of the cervix demonstrates the same concentration of cancer cells in the cervical os smear. In many cervical lesions these smears will naturally have a greater number of specific cells, as they are in reality smears taken directly from the lesions.

The ability to find the same specific cells in the vaginal smears, the external os smear, and the smear direct from the growth, and in the tissue biopsy, would appear to crystallize this study as a distinct advance in the field of early cancer diagnosis.

SUMMARY AND CONCLUSIONS

An office test to enable early uterine cancer diagnosis has been described, with an original modification in technique to facilitate greater proficiency of the test.

Two cases illustrating the use of the smear diagnosis are presented. Cancer cells are shown in both adenocarcinoma of the endometrium and squamous carcinoma of the cervix, where the diagnosis may be made by the vaginal smear, but made with greater facility by the external os smear.

The ability to demonstrate the same specific cells in the vaginal smear, the external os smear, and the smear direct from the growth and in the tissue biopsy represents a distinct advance in the field of early cancer diagnosis.

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RÉSUMÉ

Il semble possible par un simple frottis fait au bureau du médecin de faire diagnostic précoce du cancer utérin. Un frottis est fait avec les sécrétions vaginales, puis avec celles prélevées au niveau de l'oriéce externe du col utérin. Deux cas démontrent sur le frottis la présence de cellules cancéreuses. On se fie, en definitive, davantage à la valeur du prélèvement cervical. Cette possibilité nouvelle de dépister le cancer précoce représente un progrès immense dans le diagnostic des cancers uterins.

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